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Thymoma radiotherapy: a retrospective multicentre study

İpek Pınar Aral[1,2], Gonca Altınışık İnan[1,2], Fatma Betül Ayrak[1], Feyza Yaşar Daşgın[1], Nalan Arslan[1], Yıllar Lehimcioğlu[3], Fatma Yıldırım[4] , Muhammed Bülent Akıncı[5], Yılmaz Tezcan[1,2]

[1]Department of Radiation Oncology, Ankara Yıldırım Beyazıt University, Ankara, Turkey
[2]Department of Radiation Oncology, Ankara Bilkent City Hospital, Ankara, Turkey
[3]Department of Radiation Oncology, Ankara Etlik City Hospital, Ankara, Turkey
[4]Department of Pathology, Ankara BilkentCity Hospital, Ankara, Turkey
[5]Department of Medical Oncology, Ankara Bilkent City Hospital, Ankara, Turkey

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ABSTRACT

Aims: In this study, we aimed to evaluate the outcomes of thymoma patients who underwent radiotherapy (RT).

Methods: Data from thymoma patients who underwent RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital were analysed retrospectively. The primary endpoints of this study were acute and late side effects and the secondary endpoints were overall survival(OS) and disease-free survival (DFS).

Results: Data from 22 patients who received RT between 10.03.2008 and 05.10.2022 were analysed.The median follow-up time was 33 months (range: 1–76). RT-related acute toxicity was observed in 6 patients(27.3%). Late RT-related toxicity was noted in 4 patients (18%). As a late toxicity one patient (4.5%) had a secondary malignancy five years after RT.Patients younger than 40 years of age had significantly higher acute (p=0.039) and late (p=0.01) toxicity. Recurrence was observed in 7 patients (31.8%). The median DFS was 13 months (range: 1–176),the 1-year DFS was 58%, the 5-year DFS was 23%. Lower DFS was observed in patients with myasthenia gravis (MG) (p=0.018). Six patients(27.3%) died, the median OS was 33 months (range: 1–176),the 1-year OS was 84.4%, the 5-year OS was 76.7%. There was a significant correlation between performans status and OS (p=0.047).

Conclusion: Side effects were more frequently observed in patients younger than 40 years of age. Poor prognostic factors were identified as MG for DFS and poor performance status for OS. Thymoma patients have high OS, studies are needed to identify subgroups that do not require RT.

Keywords: Thymic epithelial tumours, radiotherapy, thymic carcinoma, thymoma

INTRODUCTION

Thymic epithelial tumours (TETs) are rare tumours with an incidence of 0.15 cases per 100,000 individualy.[1] They are observed at higher rates in men than women and their incidence increases with age. The World Health Organization (WHO) divides thymic malignancies into two groups: thymomas and thymic carcinomas (TCs). Thymomas are indolent tumours with a more benign course; they are usually detected incidentally and show local progression. Thymomas are divided into five subtypes (A, AB, B1, B2, and B3) and the prognosis worsens from A to B3. In addition to these classical subtypes, other subgroups such as thymoma-not otherwise specified, micronodular thymoma with lymphoid stroma, metaplastic thymoma, and lipofibroadenoma have also been documented. TCs constitute 10–12% of thymic malignancies, are more aggressive than thymomas, and have higher metastatic potential.[2-5]

Masaoka–Koga staging is commonly used for staging both thymomas and TCs.[1] This staging scheme was first described by Masaoka et al. in 1981 and later reinterpreted by Koga in 1994. Masaoka–Koga staging is based on surgical and pathological findings. The current widespread use of this staging is based on its power to predict OS.[1,3,6] Because it is a rare malignancy, multidisciplinary approaches should be at the forefront.[7] Surgery is usually the first-line treatment, but radiotherapy (RT) and less frequently chemotherapy (CT) are indicated as second-line treatments according to risk status and histology.[8] RT plays an important role in the treatment of thymoma and TC. RT is indicated for definitive purposes when surgery cannot be performed, adjuvant purposes in high-risk patients such as those with positive surgical margins, and palliative purposes in patients with recurrent or advanced-stage disease.[4,9,10] Indications for

Corresponding Author: İpek Pınar Aral, ipekpt@hotmail.com

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RT are based on non-randomized retrospective data with a limited number of patients.[7] Long-term side effects in thymoma patients are also important to consider, as long survival periods are achieved. For this reason, ongoing studies are working to identify subgroups of patients that do not require RT. In this study, we aimed to analyse the acute and late toxicities and survival of thymoma patients who received RT.

METHODS

Data from thymoma patients who received RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital were analysed retrospectively. Patient files, patient interviews, electronic system data, and RT dose-volume histograms were used in this study. Patient demographic data, pathology results, CT data, surgical details, RT information, acute side effects, late side effects, recurrence, and final status were noted. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[11]

Patient Selection

Patients at least 18 years of age with a diagnosis of pathological thymoma were included in this study. Other inclusion criteria for these patients included an (Eastern Cooperative Oncology Group) ECOG performance status of 0–4, receipt of RT, and availability of complete file data. Patients with missing files and follow-up data, as well as those with a diagnosis of TC or without a pathological diagnosis, were excluded.

Primary and Secondary Endpoints

The primary endpoints of this study were acute and late side effects, whereas the secondary endpoints were overall survival (OS) and disease free survival (DFS). DFS was defined as the time after the end of RT that a patient had no evidence of cancer. The end date for DFS was the relapse date for patients with relapse and the last control date for those without relapse. OS was defined as the time from diagnosis until death, independent of recurrence. The starting point for OS was the date of diagnosis. The OS end date was the date of death for patients who succumbed to their disease or the date of last control for patients who were alive.

Statistical Analysis

Data were analysed using SPSS version 26. The conformity of the data to a normal distribution was evaluated with the Shapiro–Wilk test; as the data were not normally distributed, parametric tests were used. The Chi-squared test and Fisher's exact test were used to analyse categorical variables. The Mann–Whitney U test was used for independent two-group analyses. The Kruskal–Wallis test was used for the analysis of 3 or more independent groups and Tukey's post hoc test was performed in cases of significance. For survival analyses, the Kaplan–Meier test was used for univariate analyses and the Cox regression test was used for multivariate analyses. The hazard ratios (HR) and 95% confidence intervals (CI) of results that were significant in our survival analyses were calculated. A HR > 1 denotes an increased relative risk compared to the reference category. The significance limit of this study was set to 0.05.

RESULTS

Data from 22 patients who received curative RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital Hospitals between 10.03.2008 and 05.10.2022 were analysed retrospectively. The median follow-up period was 33 months (range: 1–76 months). The median patient age was 47.5 years (range: 26–69 years). Six patients (27.3%) were female and 10 patients (45.5%) did not have comorbidities. With respect to patients' performance status, no patients were ECOG 4 and only 2 patients (9.1%) were ECOG 3. The median size of the largest tumour from each patient was 63 mm (range: 13–180 mm). Eight of the patients (36.4%) were diagnosed with myasthenia gravis (MG). Main vessel, pulmonary, and pericardial invasion were reported in 9 patients (40.9%), 4 patients (18.4%), and 10 patients (45.5%), respectively. Neoadjuvant CT was administered to 4 patients (18.4%) and 5 patients (22.7%) were inoperable. Neoadjuvant CT protocols were as follows: doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC; 2 patients); cisplatin plus etoposide (1 patient); and cisplatin plus cyclophosphamide (1 patient). Pathology reports were evaluated in terms of tumour resection; 8 patients (47.1%) were R0, 4 patients (23.5%) were R1, and 5 patients (29.4%) were R2. Fifty percent of the patients were B2. Staging was performed according to Masaoka–Koga guidelines; 1 patient (4.5%) was stage I; 9 patients (40.9%) were stage II, 3 patients (13.6%) were stage III, and 9 patients (40.9%) were stage IV. Of the 17 operated patients, 4 received adjuvant CT. Adjuvant CT protocols were as follows: ADOC (1 patient), cisplatin plus etoposide (1 patient), and cisplatin-cyclophosphamide (1 patient). The adjuvant CT regimen received by the remaining patient was unavailable. Patient and treatment details are summarized in **Table 1**.

Radiotherapy Details

Seventeen patients (77.3%) received adjuvant RT, 2 patients (9.1%) received definitive RT, and 3 patients (13.6%) received palliative RT. The median total RT dose was 50 Gy (range: 20–66 Gy) and the median fraction dose was 1.8 Gy (range: 1.8–4 Gy). Concurrent CT (cisplatin)

and RT were administered to 3 patients (13.6%). With respect to RT technique, 3 patients (13.6%) received two dimensional (2D) RT, 7 patients (31.8%) received three dimensional (3D) RT, 5 patients (22.7%) received intensity-modulated RT (IMRT), and 7 patients (31.8%) received volumetric modulated arc therapy (VMAT). All patients completed their RT treatment protocols. The median mean heart dose was 7.2 Gy (range: 1.1–21.3 Gy) and the median mean lung dose was 8.7 Gy (range: 3.8–15.7 Gy) (**Figure 1**) (**Table 2**).

Table 2. RT details

Parameters		N(%)
RT		
Adjuvant		17 (77.3%)
Definitive		2 (9.1%)
Palliative		3 (13.6%)
RT Total Dose	Median (range)	50 (20-66)Gy
RT Fraction dose	Median (range)	1.8 (1.8-4) Gy
Mean heart dose	Median (range)	7.2(1.1–21.3)Gy
Mean lung dose	Median (range)	8.7(3.8–15.7) Gy
Concurrent CT		
Yes		3 (13.6%)
No		19 (90.9%)
RT tecnique		
2D		3 (13.6%)
3D		7 (31.8%)
IMRT		5 (22.7)
VMAT		7 (31.8%)
Acute RT tox		
Yes		6 (27.3%)
Edema		1 (4.5%)
Esophagitis		2 (9.1%)
Pain		3 (13.6%)
No		16 (72.7%)
Late RT tox		
Yes		4 (18.2%)
Aspiration		1 (4.5%)
Lung fibrosis		1 (4.5%)
Pain		1 (4.5%)
Secondary malignancy		1 (4.5%)
No		4 (18.2%)
Missing		14 (63.6%)

Abbreviations: RT=Radiotherapy; Tox=Toxicity; CT=Chemotherapy; 2D=Two Dimensional; 3D= Three Dimensional; IMRT =Intensity Modulated Radiotherapy; VMAT=Volmetric Arc Therapy

RT-related acute toxicity was observed in 6 patients (27.3%) as follows: oedema (1 patient; 4.5%), oesophagitis (2 patients; 9.1%), and pain (3 patients; 13.6%). There were no significant relationships between acute toxicity and a diagnosis of MG (p=0.510), neoadjuvant CT (p=0.477), concurrent CT (p=0.378), total RT dose (p=0.972), RT fraction dose (p=0.056), or RT technique (p=0.713). There was a significant relationship between acute side effects and age (p=0.039; Z score: -2081). Specifically, there was a higher incidence of acute toxicity among patients less than 40 years of age (**Figure 2**).

Table 1. Patients and Treatment Details

Parameters	N(%)
Gender	
Female	6 (27.3%)
Male	16 (72.7%)
Age	
Median (range)	47.5 (26-69)
Comorbidity	
Yes	7 (31.8%)
No	15 (68.2%)
ECOG	
0	5 (22.7%)
1	8 (36.4%)
2	7 (31.8%)
3	2(9.1%)
MG	
Yes	8 (36.4%)
No	14 (63.6%)
Great Vessel Invasion	
Yes	9 (40.9%)
No	13 (59.1%)
Lung Invasion	
Yes	4 (18.4%)
No	18 (81.8%)
Pericard Invasion	
Yes	10 (45.5%)
No	12 (54.5%)
Neoadjuvant CT	
Yes	4 (18.4%)
No	18 (81.8%)
Surgery	
Yes	17 (77.3%)
No	5 (22.7%)
Resection	
R0	8(47.1%)
R1	4 (23.5%)
R2	5 (29.4%)
Thymoma Subtype	
A	2 (9.1%)
AB	2 (9.1%)
B1	3 (13.6%)
B2	11 (50%)
B3	4 (18.2%)
Masaoka Koga	
1	1 (4.5%)
2	9(40.9%)
3	3 (13.6%)
4	9(40.9%)
Adjuvant CT	
Yes	4 (18.2%)
No	13 (59.1%)
Recurrrence	
Yes	7 (31.8%)
No	15 (68.2%)
Recurrrence Site	
Local	3 (13.6%)
Regional	1 (4.5%)
Distance	2 (9.1%)
Local + Distance	1 (4.5%)
Last Status	
Ex	6 (27.3%)
Alive	16 (72.7%)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; MG=myastenia gravis; CT= Chemotherapy

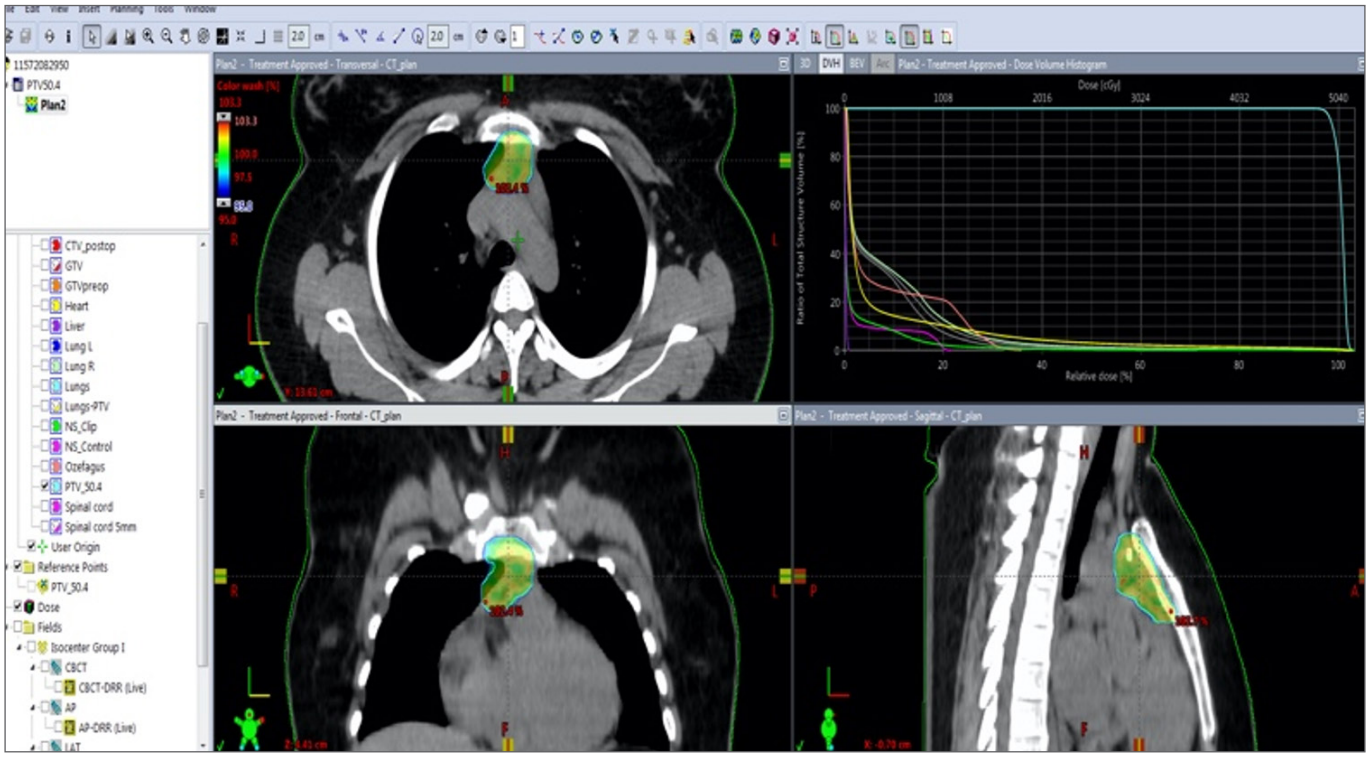

Figure 1. RT- planning image of a thymoma patient

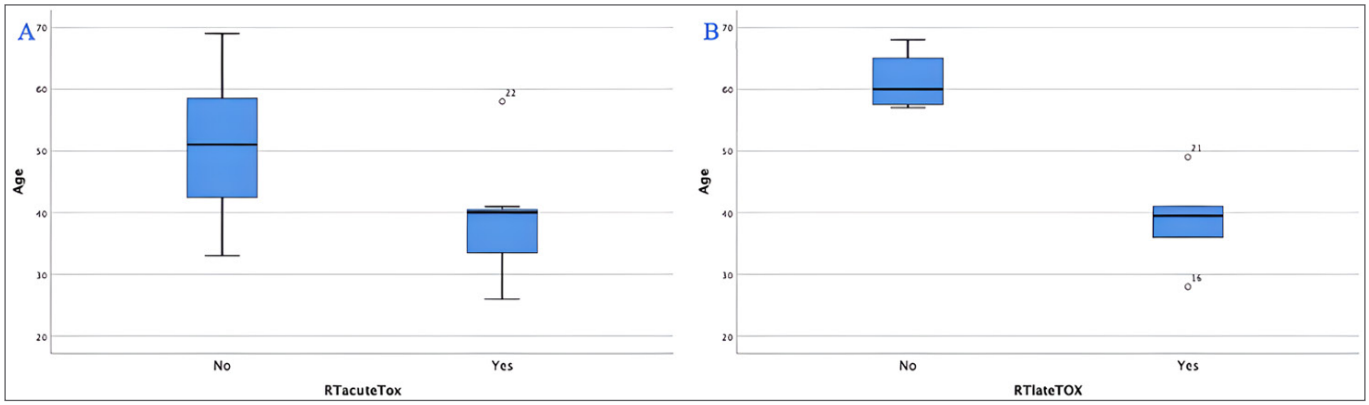

Figure 2. Patients younger than 40 years of age had significantly higher acute (A) and late toxicity (B).

Information on late toxicity associated with RT is available in only 8 (36.4%) patients, of which 4 reported late toxicity. However information on late toxicity associated with RT were not available for 14 patients (63.6%). The following late side effects were observed: chronic aspiration and dysphagia (1 patient; 4.5%), lung fibrosis (1 patient; 4.5%), chronic pain (1 patient; 4.5%), and secondary malignancy (1 patient; 4.5%). As a secondary malignancy, breast cancer was observed in our 36-year-old female patient 5 years after the treatment. There were no significant relationships between late toxicity and a diagnosis of MG (p=0.667), neoadjuvant CT (p=0.333), concurrent CT (p=0.610), total RT dose (p=0.380), RT fraction dose (p=0.516), or RT technique (p=0.383). There was a significant relationship between late side effects and age (p=0.011; Z score: -2558). Specifically, late toxicity was more prevalent among patients less than 40 years of age (**Figure 2**).

Details of DFS Analysis

Recurrence was observed in 7 patients (31.8%) (**Table 3**). The median DFS was 13 months (range: 1–176 months), the 1-year DFS was 58%, and the 5-year DFS was 23%. Lower DFS was observed among patients with MG (p=0.018; HR: 6.7; 95% CI: 1.2–36.7). There were no significant relationships between DFS and age (p=0.954), comorbidity status (p=0.426), ECOG performance status (p=0.717), great vessel invasion (p=0.326), pulmonary invasion (p=0.136), pericardial invasion (p=0.740), tumour size (p=0.742), neoadjuvant CT (p=0.837), surgery status (p=0.643), resection status (R0, R1, R2) (p=0.374), pathological subtype (A–B3) (p=0.964), stage (p=0.171), adjuvant CT (p=0.058), concurrent CT (p=0.651), RT technique (p=0.894), total RT dose (p=0.367), mean heart dose (p=0.383), or mean lung dose (p=0.625) (**Figure 3**).

Table 3. Patient's Details

Patients	Age Gender ECOG	Co.	MG	Surgery	Stage	CT	RT	RT tox	Recurrence DFS	Last Status OS
1	57, M ECOG 1	DM, HT, BPH	No	Operated R0 TS: 30 mm	Stage 1 , B2 (no total thymectomy)	None	50 / 2Gy IMRT	None	Rec: No DFS: 11.5 mo	Alive OS: 11.5 mo
2	44, M ECOG 0	None	Yes	Operated, R0 TS: 36 mm	Stage 2 , B2 GV invasion : +	None	50 / 2Gy IMRT	Acute: none Late: NS	Rec: No DFS: 2.5 mo	Ex OS: 11.5 mo
3	46, F ECOG 1	None	No	Operated R1 TS: 67 mm	Stage 2 , B2 Pericard inv: +	CCT Cisp	54/2 Gy VMAT	Acute : none Late: none	Rec: No DFS: 5.45 mo	Alive OS: 5.45 mo
4	39, M ECOG 1	None	No	Operated R2 TS: 23 mm	Stage 2 , B1	CCT Cisp	45/1.8 Gy IMRT	Acute : Upper Ext Edema Late: none	Rec: No DFS: 7.16 mo	Alive OS: 7.16 mo
5	62, M ECOG 2	HT BPH	No	Operated R0 TS: 143 mm	Stage 2 , A	None	50 / 2Gy VMAT	Acute: None Late: None	Rec: No DFS: 19.0 mo	Alive OS: 19.0 mo
6	68, M ECOG 2	HT, DM	No	Operated R0 TS: 41 mm	Stage 2 , B3	None	45 / 3 Gy VMAT	Acute: None Late: None	Rec: No DFS: 24.6 mo	Alive OS: 24.6 mo
7	28, M ECOG 0	None	No	Operated R1 TS: 67 mm	Stage 2 , B3	None	54/ 2 Gy 3D	Acute: Pain Late: Lung Fibrosis	Rec: No DFS: 104 mo	Alive OS: 104 mo
8	60, M ECOG 1	None	No	Operated R0 TS: 65 mm	Stage 2 , AB GV inv: +	None	50 Gy /2 Gy 3D	Acute: None Late: None	Rec: No DFS: 131.9 mo	Alive OS: 131.9 mo
9	26, F ECOG 0	None	Yes	Operated R0 TS: 25 mm	Stage 2 , B2	None	50.4/1.8 VMAT	Acute: Pain Late: NS	Rec: yes (local) DFS: 5.72 mo	Alive OS: 7.70 mo
10	33, M ECOG 1	None	No	Operated R0 TS: 62 mm	Stage 2 , B3	None	50.4/1.8 3D	Acute: None Late: None	Rec: yes (local + distant) DFS: 9.95 mo	Alive OS: 11.04 mo
11	53, M ECOG 2	None	No	Operated R2 TS: 122 mm	Stage 3 , AB GV inv: + Pericard inv: +	Neoadj: ADOC	66/2 Gy IMRT	Acute: None Late: None	Rec: No DFS: 45.04 mo	Alive OS: 45.04 mo
12	53, F ECOG 1	None	Yes	Inoperable TS: 80 mm	Stage 3 , B1 GV inv: +	None	50 / 2 Gy 2D	Acute: Pain Late: NS	Rec: Yes (distant) DFS: 39.0 mo	Ex OS: 42.0 mo
13	40, F ECOG 3	None	Yes	Operated R1 TS: 35 mm	Stage 3 , B2 GV inv: + Pericard inv: +	None	50.4/1.8 3D	Acute: Esophagitis Late: Chronic aspiration	Rec: Yes (local) DFS: 12.25 mo	Ex OS: 12.42 mo
14	69, M ECOG 3	None	No	Inoperable TS: 180 mm	Stage 4, GV inv: +	None	36 / 3 Gy VMAT	Acute: None Late: None	Progression DFS: 1 mo	Ex OS: 1 mo
15	40, M ECOG 2	None	No	Inoperable TS: 100 mm	Stage 4,B2 GV inv: + Pericard inv: +	Neoadj: Cisp + Cyclo	60 /2 Gy 3D	Acute: Esophagitis Late: NS	Rec: No DFS: 9.59 mo	Alive OS: 9.59 mo
16	69, F ECOG 2	HT	No	Operated R0 TS: 170 mm	Stage 4, A Lung inv: +	None	30/3 Gy VMAT	Acute: None Late: NS	Rec: No DFS: 48.33 mo	Alive OS: 48.33 mo
17	51, M ECOG 0	No	Yes	Operated R1 TS: 110 mm	Stage 4, B3 Pericard inv: +	CCT Cisp	54/2 Gy VMAT	Acute: None Late: NS	Rec: No DFS: 71.7 mo	Alive OS: 71.7 mo
18	41, M ECOG 2	No	Yes	Inoperable TS: 110 mm	Stage 4, B2 Pericard inv: +	Neoadj: Cisp + etoposide	20/4 Gy 3D	Acute: None Late: NS	Rec: No DFS: 128.1 mo	Alive OS: 128.1 mo
19	46, M ECOG 1	None	No	Operated TS: 45 mm	Stage 4, B2 Lung inv: +	None	50/2 Gy 2D	Acute: None Late: NS	Rec: No DFS: 166.6 mo	Alive OS: 166.6 mo
20	49, M ECOG 1	None	No	Operated R2 TS: 45 mm	Stage 4, Lung inv: + Pericard inv: +	Neoadj: ADOC Adj: Carbo +pacli	30/3 Gy 2D	Acute: None Late: Pain	Rec: Yes (distant) DFS: 93.3 mo	Alive OS: 114.2 mo
21	54, M ECOG 2	None	Yes	Operated R2 TS: 60 mm	Stage 4, B1 GV inv: +	Adj CT	66 /2 Gy IMRT	Acute: None Late: NS	Rec: Yes (local) DFS: 176.4 mo	Ex OS: 177.1 mo
22	36, F ECOG 0	None	Yes	Operated R2 TS: 65 mm	Lung inv: + Pericard inv: +	Adj CT: ADOC	60 /2 Gy 3D	Acute: None Late: Secondary Malignancy, Breast Cancer, 5 years after RT	Rec: Yes (local) DFS: 6.4 mo	Alive OS: 126,36 mo

Abbreviations: ECOG=Eastern Cooperative Oncology Group; F=Female; M= Male; Co=Comorbidity; MG= myastenia gravis; CT=Chemotherapy, RT=Radiotherapy; CCT=Concurrent Chemotherapy; mo=months; DFS=Disease free survey; OS=Overall Survey; Tox=Toxicity; DM=Diabetes Mellitus; HT=Hypertension; BPH=Benign Prostatic Hyperplasia; IMRT= Intensity Modulated Radiotherapy; VMAT=Volmetric Arc Therapy, TS= Tumor Size; ADOC=doxorubicin, cisplatin, vincristine , cyclophosphamide; NS=Not Specified;

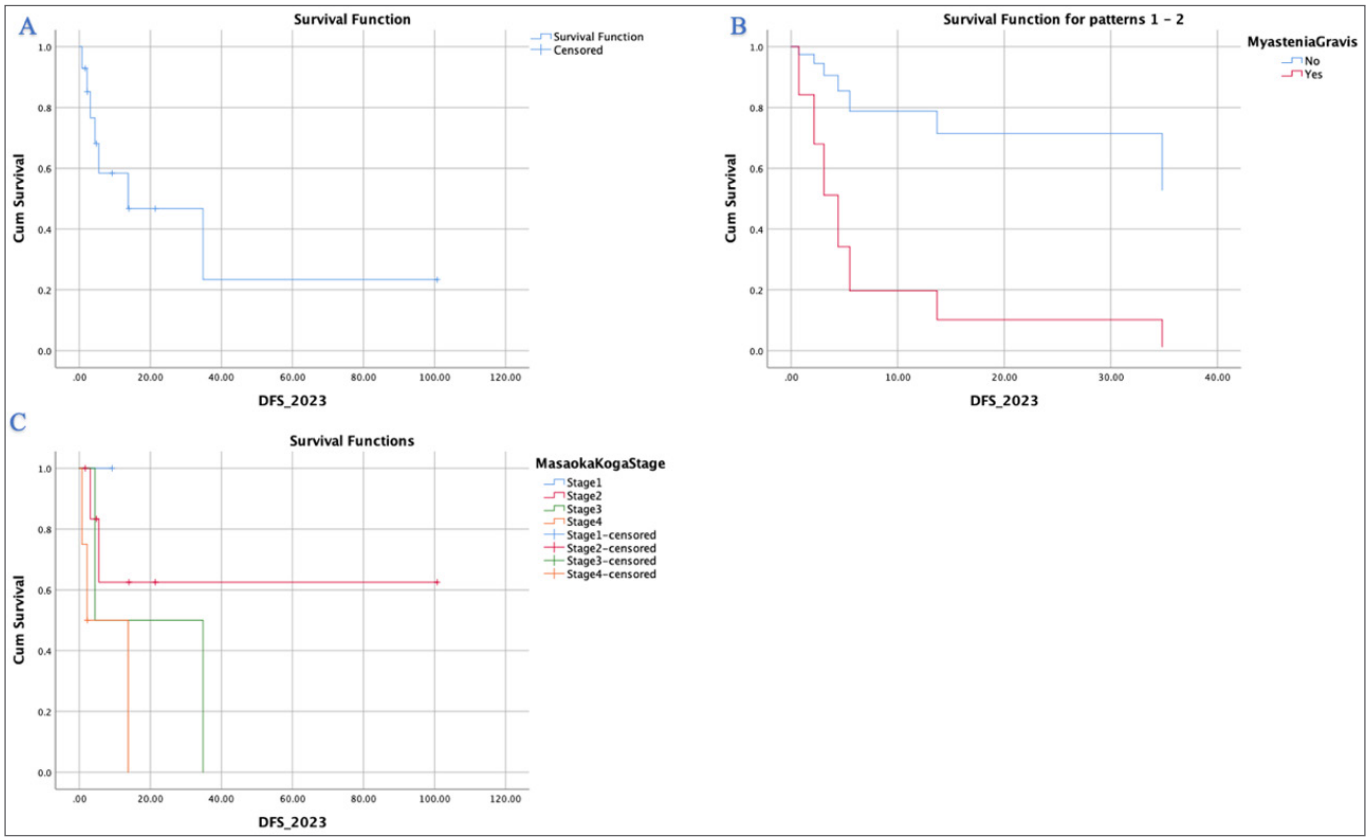

Figure 3. A. Image of DFS's Kaplan Meier Analysis; B. Lower DFS was observed in patients with MG (p=0.018); C. The relationship between Masaoka Koga Stage and DFS was not statistically significant.

Details of OS Analysis

During the follow-up period, 6 patients (27.3%) died (**Table 3**). The median OS was 33 months (range: 1–176 months). The 1-year OS was 84.4% and the 5-year OS was 76.7%. There were no significant relationships between OS and sex (p=0.482), age (p=0.633), comorbidity status (p=0.860), MG diagnosis (p=0.428), great vessel invasion (p =0.098), pulmonary invasion (p=0.711), pericardial invasion (p=0.462), tumour size (p=0.551), neoadjuvant CT (p=0.838), surgery status (p=0.427), resection status (R0, R1, R2) (p=0.703), pathological subtype (A–B3) (p=0.514), stage (p=0.363), adjuvant CT (p=0.327), concurrent CT (p=0.649); RT technique (p=0.763), total RT dose (p=0.765), mean heart dose (p=0.837), or mean lung dose (p=0.580).

There was a significant correlation between ECOG performance status and OS, in that patients with good general condition had better OS (p=0.047; HR: 18.2; 95% CI: 1.02–32.2). Significantly higher OS was achieved in patients without complaints (ECOG 0). Specifically, the median OS was 71 months (range: 2–126 months), 26 months (range: 5–166 months), and 44 months (range: 9–177 months) among patients with ECOG performance statuses of 0, 1, and 2, respectively (**Figure 4**).

DISCUSSION

Consistent with the literature, we observed high RT compliance and long survival periods among thymoma patients in our study. One patient (4.5%) in our series presented with secondary malignancy as a late side effect. Another remarkable result is that both acute and late side effects were significantly higher in patients under 40 years of age. However, OS and DFS values were not significantly different in patients younger than 40 years of age vs. those older than 40 years of age. Poor prognostic factors were identified as MG and poor performance status for DFS and OS, respectively.

Thymomas typically affect men and women equally but a higher incidence has been observed in males in some case series. In the literature, two different peak age ranges have been reported, including 45–55 years of age and the seventh decade of life.[12] There were 16 male patients (72.7%) in our series, representing a significant male predominance. The median patient age was 47.5 years (range: 26–69 years). Approximately half of thymoma patients have a diagnosis of MG and thymomas are observed in 15% of MG patients.[13] Eight (36.4%) of our patients had a diagnosis of MG. No significant differences were observed in patients with MG in terms of acute toxicity, late toxicity, or OS. However, DFS was significantly lower in MG patients.

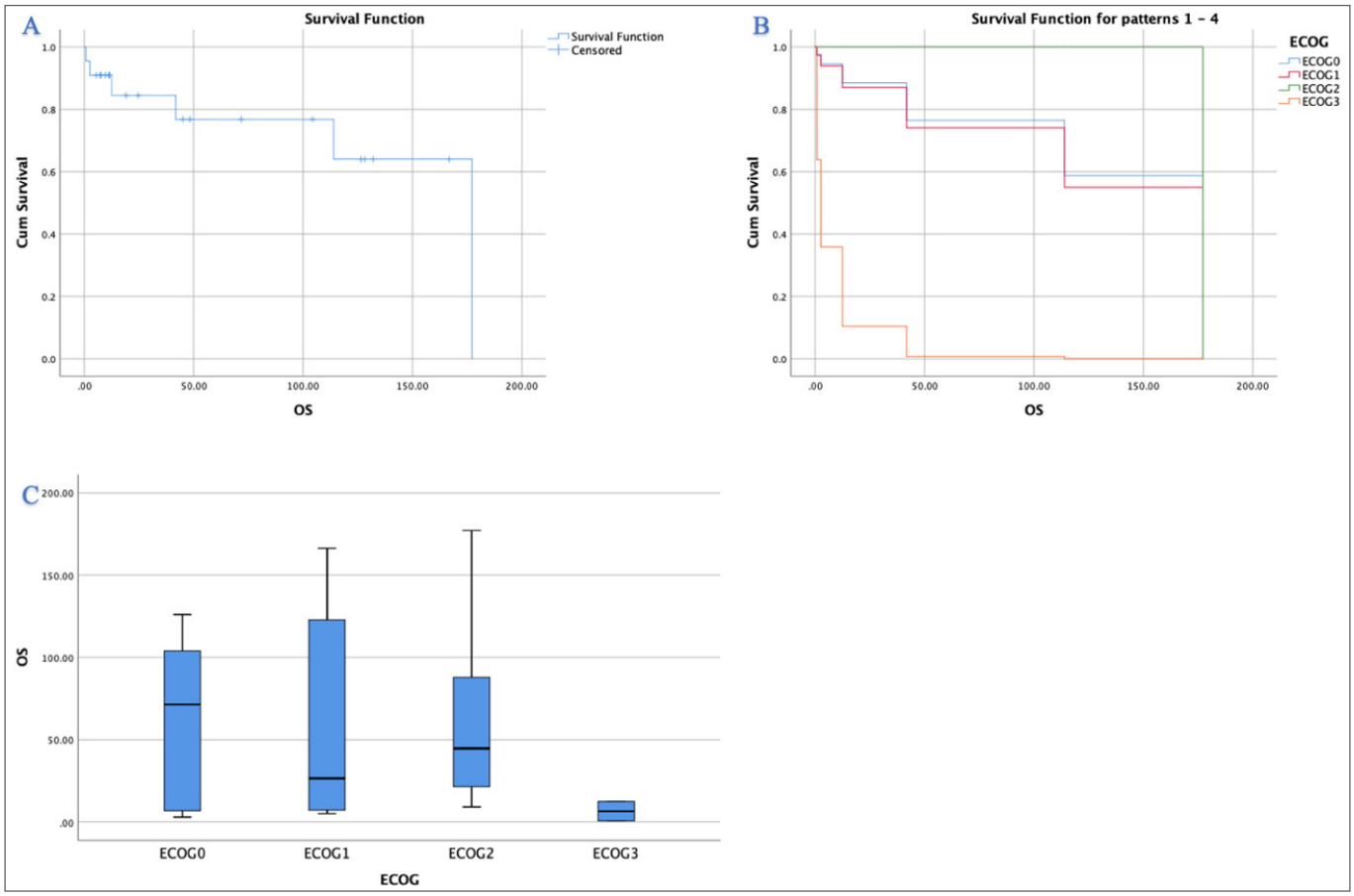

Figure 4. A. Image of OS Kaplan Meier Analysis; B. Lower OS was observed in patients with poor performance status; C. Box blot image evaluating the ECOG - OS relationship.

TCs represent a small fraction of TETs. Pathologically, the distinction between TC and atypical thymoma is important; atypical thymomas differ from TCs in terms of treatment approach and prognosis. The median survival for patients with TC is 6.6 years.[14] Atypical thymoma is a remarkable definition detailed in the 2021 WHO Classification.[5] According to this staging scheme, atypical thymoma is a variant of group A thymomas. In the present study, no atypical variants were noted in the pathology reports. There was also no significant relationship between thymoma histological subtype and survival.

An important current issue in the field of TET therapy is the identification of patient subgroups that do not require RT.[4] RT indications for TET should be evaluated separately for thymoma and TC. Surgery is usually the initial treatment for these patients. Patients who are candidates for surgery should be evaluated in an experienced RT clinic to determine if they should receive adjuvant RT. Adjuvant RT is not indicated for all thymic epithelial malignancies. According to the European Society for Medical Oncology (ESMO) 2021 guidelines, thymoma patients with PT1aR0 tumours of the A–B1 subtypes and without massive capsular invasion can be observed and adjuvant RT is not indicated. However, postoperative RT (PORT) is indicated in cases of B2–3 tumours or those with massive capsular invasion, even at early stages. For TCs, PORT is recommended for all patients except selected patients with pT1aR0 tumours.[15] In addition to ESMO, the Oncologic Group for the Study of Lung Cancer/Spanish Society of Radiation Oncology (GOECP/SEOR) published another set of important RT guidelines, last updated in 2021. In the GOECP/SEOR 2021 guidelines, the indications for RT are determined according to Masaoka–Koga staging. Specifically, patients for whom PORT is not indicated include those with stage I and stage IIA tumours with R0 resection.16 There was only 1 patient with a stage I tumour (R0, B2) in our study. The patient was evaluated by the multidisciplinary tumour council. The patient's tumour underwent R0 resection and the subtype was B2, but total thymectomy was not performed. Therefore, adjuvant RT was administered.

According to current guidelines, adjuvant RT is indicated for patients with Masaoka–Koga stage IIB and III tumours.[15,16] The necessity of adjuvant RT for this disease in which high OS can be obtained is controversial. According to a study by Song et al.[17] adjuvant RT does not contribute to overall survival in patients with a completely resected stage II thymoma. Additionally, in

an analysis of 65 patients with complete resected stage III (Masaoka–Koga) tumours, the 5- and 10-year OS rates were reported as 91.7% and 71.6%, respectively. In this study, PORT reduced local recurrence but did not contribute to OS.[3] In patients with unresectable or debulked stage III thymoma, the contribution of definitive RT has been reported in the literature and identified as an independent prognostic factor for OS.[18] In an Italian study that evaluated 183 thymoma patients from three different centres, the lowest DFS and OS rates were observed in patients with incompletely resected thymomas. Thus, RT appears to contribute to patients with stage II-III thymoma without complete resection.[7] Further, in a Surveillance, Epidemiology, and End Results program analysis of 2,236 thymoma patients published by Mou et al.[9] in 2020, PORT was recommended for all patients over 60 years of age and who had Masaoka–Koga stage III and IV tumours. However, no strong evidence for the contribution of PORT has been reported in patients with stage II thymoma.[9] In summary, whether or not adjuvant RT should be administered to patients with stage II-III thymoma is controversial, especially in cases of complete resection. In these patients, RT dose varies between 50 and 66 Gy depending on the type of surgery received, residual status, and pathological subtype.

The RT field for thymoma patients is the anterior mediastinum proximal to the heart. For every 1 Gy increase in the mean heart dose, the risk of major cardiac events increases by 7.4%.[19] In our study, the median mean heart dose was 7.2 Gy (range: 1.1–21.3 Gy). No significant relationship was found between mean heart dose and OS, but we predict that RT increases patients' risks of major cardiac events. This rate is a serious late side effect for this disease, which carries a long life expectancy. Thus, the balance of insufficient and over-treatment needs to be correctly evaluated for stage IIB and III thymoma patients.

For stage II and III thymoma patients, an accurate assessment of the balance between local recurrence-associated problems in patients who do not receive RT and the long-term side effects associated with RT—particularly long-term cardiac effects—is needed. For this purpose, "RADIORYTHMIC", a phase III randomized trial that aimed to evaluate the necessity of adjuvant RT in patients with Masaoka–Koga stage IIB/III thymoma, was initiated. In this study, patients with completely resected tumours were randomized to adjuvant RT vs. observation. A total of 50–54 Gy of IMRT or proton therapy are being administered to patients in the RT arm. The results of this study are expected to be presented in 2028. This trial is the first prospective randomized phase III study of PORT in thymoma patients.[6] In our study, nine patients had stage II tumours and two of these patients relapsed. In both patients, R0 resection was achieved and 50.4 Gy of adjuvant RT was administered. In these two patients with local relapse, subtype was the only remarkable unfavourable prognostic factor, as one patient had a B2 tumour and the other patient had a B3 tumour.

In addition to cardiac toxicity, pulmonary fibrosis is another important RT-related toxicity. Radiation pneumonitis and pulmonary fibrosis may be observed as acute and late RT-related side effects, respectively. Radiation pneumonia is also one of the most frequently observed RT-related toxicities. In an analysis by Kirakli et al.[2] radiation pneumonia was reported in 52% of patients with grade 1 and 2 tumours. However, in an Italian study, there were no significant differences in terms of side effects between patients in the PORT and observation arms.[7] In our study, RT-related late toxicity was noted in 8 patients (36.4%), but no such data were available for 14 patients (63.6%). Thus, cancer registries should contain more detailed data about the long-term side effects of RT, especially for patients with rare diseases for whom long survival periods are expected. Among the patients in our study for whom these data were available, late side effects were as follows: chronic aspiration and dysphagia (1 patient; 4.5%), pulmonary fibrosis (1 patient; 4.5%), chronic pain (1 patient; 4.5%), and secondary malignancy (1 patient; 4.5%).

Modern RT techniques (e.g. IMRT, image-guided RT [IGRT], and four dimensional (4D) computed tomography) should be used in thymoma patients because the RT field is adjacent to many vital organs.[4] In the literature, RT techniques such as 3D approaches, IMRT, IGRT, VMAT, stereotactic body RT [SBRT], and proton therapy have been administered to thymoma patients.[20] In a prospective analysis of proton therapy for TET patients, Mercado et al.[21] reported a 3% local recurrence rate after a median of 13 months of follow-up. In addition, no patients had grade 3 or higher side effects. Although side effects are reduced in patients who receive proton therapy, standard IMRT techniques are more accessible to patients. With IMRT techniques, effective doses can be applied to target volumes while protecting surrounding organs. Stereotactic radiosurgery for TET patients is experimental and there is limited available data in the literature. In a prospective study by Hao et al.[22] in which SBRT was administered to 39 lesions in 32 patients, the response rate was 96.9% and the local control rate was 81.25%. Thus, this study concluded that SBRT may be an alternative for patients with unresectable tumours who are not candidates for conventional RT. However, SBRT is not the standard approach for thymoma patients.[22] In our case series, no patients preferred SBRT. IMRT/VMAT was administered to the most of the patients.

The target volume for thymoma and TC includes the surgical bed and risk area and there is no elective nodal irradiation.4 Gross tumour volume is defined by positron emission tomography fusion imaging and the clinical target volume margin is usually 5 mm.[16] Typically, conventional fraction doses of 1.8 and 2.0 Gy are preferred. Johnstone et al.[4] suggested the following doses in their research presented in 2022, 45–50.4 Gy for R0 patients, 50–54 Gy for R1 patients, and 60–70 Gy for R2 and inoperable patients. The National Comprehensive Cancer Network (NCCN) and GOECP/SEOR guidelines also recommend the same doses.[16,23] However, doses below 40 Gy are also under investigation in early-stage thymoma patients and those with completely resected tumours.[10,24] In addition, although some approaches recommend doses above 56 Gy in patients with R2 resection or unresectable tumours, there is no consensus on this issue.[25] If concurrent CT is to be administered, 54 Gy is also an effective dose and is often preferred.[26] In our study, the median dose was 50 Gy and only 3 patients (13.6%) were treated with concurrent CT. There were no significant relationships between RT technique and acute side effects or survival.

In patients with resectable thymomas, the first treatment choice is surgery. The optimal surgery is en bloc resection of the entire thymus and peritumoral adipose tissue. Minimally invasive surgical procedures should only be attempted by experienced thoracic surgeons for small tumours but they are not recommended as standard approaches. In cases of locally advanced disease, the surrounding organs (cardiac main vessels, lung parenchyma, etc.) into which the tumour has invaded should also be resected. If maximal reduction surgery is performed, surgical risk areas should be marked with clips.[15] Clips are important tools that enhance compliance between surgeons and radiation oncologists. In our study, 17 patients (77.3%) underwent surgery and R0 resection was achieved in 8 patients (47.1%).

The majority of TET RT data are based on studies of TC wherein CT response rates are low. NCCN guidelines recommend carboplatin/paclitaxel as a first-line therapy, with an overall response rate of 22–36%. A total of six additional defined protocols can be administered. ADOC, administered to 3 patients (13.6%) in our case series, is also effective in thymic tumours but is more toxic than carboplatin/paclitaxel. Second-line systemic therapy can be used in patients who cannot tolerate or progress from first-line therapy. Second-line systemic treatment options include sunitinib, pemetrexed, everolimus, paclitaxel, gemcitabine with or without capecitabine, 5-fluorouracil, etoposide, ifosfamide, lenvatinib, and pembrolizumab. Response rates were 22.5% with pembrolizumab but severe immune toxicity rates (15%) were observed.[23]

Study Limitations

The most important limitation of the study is its retrospective nature. In addition, CT preference and RT dose/technique were heterogeneous. For thymoma, which is a rare disease, there is a need for prospective studies with a large series of patients using standard treatments.

CONCLUSION

Side effects were more frequently observed in patients younger than 40 years of age. Poor prognostic factors were identified as MG for DFS and poor performance status for OS. Thymoma patients have high OS, studies are needed to identify subgroups that do not require RT. The patients were evaluated with a multidisciplinary approach before their treatment commenced.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 11.01.2023, Decision No: E1-23-3183).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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